Enantioselective Synthesis of Natural Dibenzylbutyrolactone Lignans (-)-Enterolactone, (-)-Hinokinin, (-)-Pluviatolide, (-)-Enterodiol, and Furofuran Lignan (-)-Eudesmin via Tandem Conjugate Addition to γ-Alkoxybutenolides

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Enantioselective Synthesis of Natural Dibenzylbutyrolactone Lignans (−)-Enterolactone, (−)-Hinokinin, (−)-Pluviatolide, (−)-Enterodiol, and Furofuran Lignan (−)-Eudesmin via Tandem Conjugate Addition to γ-Alkoxybutenolides[1,2]

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A general and efficient method is described for the asymmetric synthesis of a variety of lignans. 5-(Menthyloxy)-2(5*H*)-furanones **5** proved to be excellent chiral synthons in this respect and could be transformed with complete stereoselectivity into a number of lignans. The addition of lithiated dithianes **7** to enantiomerically pure butenolides **5** was followed by quenching of the resulting lactone enolate anions with a benzylbromide (**9**) or with an aldehyde (**6**). This tandem addition quenching procedure gave the diastereomerically pure adducts **11**, **26**, or **27** in 50−67% yield, with a carbon skeleton as found in most natural lignans. As examples of the wide applicability of this method, the syntheses of the enantiomerically pure natural lignans (−)-hinokinin (**23b**), (−)-enterolactone (**24a**), (−)-pluviatolide (**24c**), and (−)-enterodiol (**25**) in overall yields of 29−37% from **5a** and (−)-eudesmin (**30**) in 16% overall yield from **5b** are described.

Introduction

Lignans are a class of natural compounds that can be found in nearly any plant on the earth,[3] and these compounds have shown a range of biological activities. An enormous variety of lignans are known today, but in general the following structural classes are defined: dibenzylbutanes such as dibenzylbutyrolactones **1** and dioxabicyclo[3.3.0]octanes **2**, 1-aryltetralin lignans **3**, and dibenzocyclooctadienes **4** (Figure 1).[4]

Since the discovery that members of lignans of the structural type **1**, like enterolactone and enterodiol, can be isolated from the urine of different mammals, which was in contrast with the opinion that they were plant metabolites only,[5] interest in dibenzylbutyrolactones has grown rapidly. These lignans have various biological activities such as antitumor activity,[6] platelet-activating factor (PAF) antagonists,[7] sodium selective diuretic properties,[8] and inhibitory effects on microsomal monooxygenases in insects.[9] Enterolactone production seems to

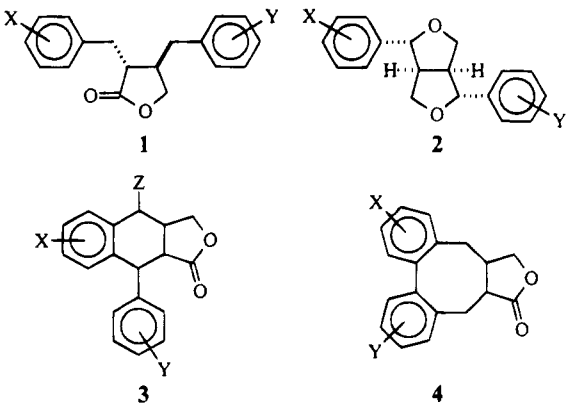

Figure 1.

be under endocrine control,[10] and it depresses oestrogen-stimulated RNA synthesis.[11] Natural enterolactone and enterodiol are racemic and they are unique in lacking para substitution in the benzylic groups.[12] Furthermore they are known to have a dietary origin.

(−)-Hinokinin and (−)-pluviatolide also belong to the structural type **1** lignans whereas (−)-eudesmin is a typical member of class **2** lignans. First discovered in 1896 eudesmin has been isolated from many plant species.[13] It displays cAMP phosphodiesterase inhibitory activity.[3,4] Podophyllotoxin and analogs, the most prominent members of type **3** lignans, have been used as anticancer and antiviral agents[14] whereas anticancer activity has also been found for dibenzocyclooctadiene lignans **4**.

A number of strategies, mainly based on alkylation or Michael addition to butenolides, to achieve stereocontrolled synthesis of various structural classes of lignans have been developed.[2,4,14−17] Methodology for the prepa-

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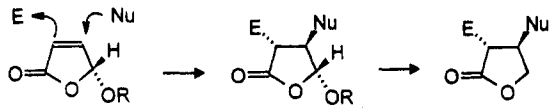
Scheme 1



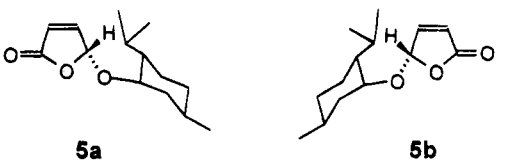
ration of dibenzylbutane lignans include Stobbe condensation of aromatic aldehydes with succinic acid esters,[18] oxidative coupling of propionic acid derivatives,[19] nitrile oxide cycloaddition,[16] malonic ester substitution[20] and reductive cyclization of α-bromo allylic esters.[21]

Asymmetric syntheses of dibenzylbutyrolactone lignans by diastereoselective alkylation or aldol reactions of monobenzyl-substituted butyrolactones have been particularly successful.[4,22] The required optically active butyrolactones are accessible from, for example, *l*-glutamic acid,[22] via resolution of alkylated succinic esters,[23] and from alkenyl sulfoxides,[24] whereas Posner et al.[25] used the conjugate addition of benzyl Grignard reagents to a chiral *p*-toluenesulfinyl butenolide as a key step. Recently routes to enantiomerically pure dibenzylbutane lignans were developed by Magnusson et al.[15] and Sibi et al.[16] These routes were based, respectively, on conjugate addition to chiral dihydrofuryl ketones and a nitrile oxide cycloaddition–lipase mediated resolution procedure.

Elegant routes to aryltetralin and dibenzocyclooctadiene lignans using chiral oxazolines have been developed by Meyers and co-workers.[26] The chromium carbene route, recently reported by Miller and Hegedus,[27] offers a valuable alternative.

Improvement of current methodology for the total synthesis of enantiomerically pure lignans is however highly warranted[14,28] as several routes are rather lengthy[29] or multistep syntheses of chiral starting materials are required whereas modest stereoselectivities are found in several cases. Our goal was to develop a short and flexible route based on readily available chiral synthons, with absolute stereocontrol, to various structural classes of lignans.

This paper presents full details[1,2] of our new approach to dibenzylbutyrolactone lignans and dioxabicyclo[3.3.0]-octane lignans based on tandem conjugate addition–alkylation of enantiomerically pure γ-alkoxy-2(5*H*)-furanones (Scheme 1). Employing a benzylic nucleophile and a benzylic electrophile, uniformly high diastereocontrol is observed in the tandem conjugate addition–quenching procedures. Subsequent reduction with removal of the γ-alkoxy substituent results in a variety of lignans in enantiomerically pure form. A very attractive feature of this approach is that virtually all aromatic substitution patterns found in natural lignans can be matched synthetically.



5a (5R)-(l)menthyloxy-2(5H)-furanone

5b (5S)-(d)menthyloxy-2(5H)-furanone

Figure 2.

Results and Discussion

The chiral butenolides (5*R*) (**5a**) and (5*S*)-(menthyloxy)-2(5*H*)-furanone (**5b**) (Figure 2) are the key synthons[30] in the methodology described here. Enantiomerically pure **5a** and **5b** are readily available on a multigram scale from furfural and *l*- or *d*-menthol, respectively, involving a remarkable second-order asymmetric transformation.[30]

Butenolides **5a** and **5b** have proven to be extremely valuable as chiral dienophile[31] and Michael acceptor,[32] generally providing products with enantiomeric excesses (ee) exceeding 99%, after removal of the auxiliary group *d*- or *l*-menthol.

An important feature is the easy removal, and in most cases recovery in high yield, of the chiral auxiliary alcohol *d*- or *l*-menthol by simple acetal hydrolysis after the asymmetric transformations of **5**. Previously we have shown that several carbon nucleophiles enter trans-diastereoselective (with respect to the 5-menthyloxy moiety) in conjugate addition reactions to butenolides **5a** and **5b**.[33] We envisaged that the basic lignan carbon framework, i.e., the dibenzylbutyrolactone structure, might be formed in a one-pot procedure by conjugate addition of benzylic dithioacetal anions to **5a** followed by quenching of the resulting lactone enolate anion **10** with an appropriate benzylic electrophile (Schemes 1 and 3). The dithianes **7a–7c** were prepared from the corresponding aldehydes following a literature procedure (Scheme 2).[34] Stirring a solution of the benzaldehydes **6** with 2 equiv of thiophenol and a catalytic amount of $AlCl_3$ gave

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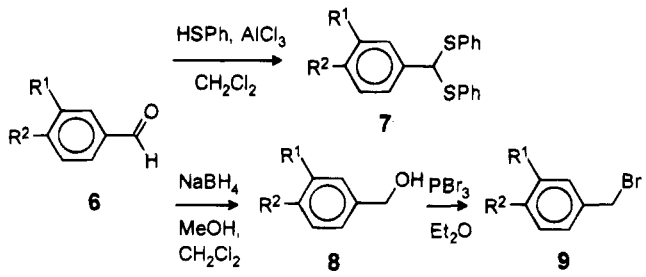
Scheme 2



6a R^1= OBn, R^2= H
6b R^1,R^2= OCH_2O
6c R^1=OMe, R^2= OBn
6d R^1=R^2= OMe
6e R^1= OBn, R^2= OMe

Table 1. Yields of the Conversion of Benzaldehydes 6 to the Corresponding Dithianes 7 or Bromides 9 (Scheme 2)

entry	aldehyde	R^1	R^2	dithiane	bromide	yield,[a] %
1	**6a**	OBn	H	**7a**		81
2	**6b**	OCH_2O		**7b**		90
3	**6d**	OMe	OMe	**7d**		80
4	**6e**	OBn	OMe	**7e**		88
5	**6a**	OBn	H		**9a**	80
6	**6b**	OCH_2O			**9b**	73
7	**6c**	OMe	OBn		**9c**	84
8	**6d**	OMe	OMe		**9d**	81

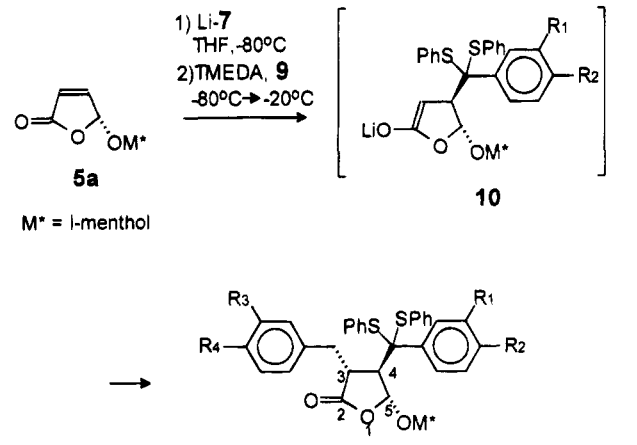
[a] Yields are of isolated pure products after crystallization.

the dithianes **7** in high yields. The benzyl bromides **9** were prepared in high yields from the corresponding aromatic aldehydes **6** in two steps, by modification of a reported procedure.[35] In the first step the aldehydes were reduced to the alcohols **8** with $NaBH_4$ in methanol and dichloromethane and subsequently converted to benzyl bromides **9** with PBr_3 in Et_2O. The results of the conversion of benzaldehydes **5** to the corresponding dithianes **7** or benzyl bromides **9** are summarized in Table 1.

The anions of dithioacetals **7** were generated by treatment of a solution of the dithioacetal in THF with *n*-butyllithium at −20 °C. The conjugate addition (Scheme 3) of lithiated dithianes **7a,b,d** to **5a** at −80 °C was followed by quenching of the resulting lactone enolate anion **10** with benzyl bromides **9a,b,c,d** at −80 to −30 °C to yield the dibenzylbutyrolactones **11** with a complete lignan skeleton.[36] The results of this tandem conjugate addition−alkylation reaction to butenolide **5a** are summarized in Scheme 3.[37]

Single diastereoisomers are observed in all cases, indicating complete stereocontrol in both the conjugate addition and enolate alkylation steps. According to ^1H and ^{13}C NMR, diastereoselectivities exceed 98%. As expected[32,33] the bulky menthyloxy moiety in **5** directs the dithioacetal anion to anti attack with respect to the

Scheme 3



γ-alkoxy substituent. Quenching of the resulting lactone enolate anion **10** with benzyl bromides **9** leads to the 3,4-trans dibenzylated product due to the steric effect of the aryldithiane moiety at the 4-position. As a consequence, the lactones **11** have the (3*R*,4*R*)-configuration as is found in most natural dibenzylbutane lignans.[4] All the lactones **11** showed coupling constants $J_{H4,H5} < 0.5$ Hz. The small coupling constants for the acetal proton (H_5) in the ^1H NMR spectra are very distinctive for the trans relationship between the substituents at C_4 and C_5. For cis-4,5-disubstituted lactones, coupling constant $J_{H4,H5}$ in the range of 3−6 Hz are observed.[33,38] The trans relationship of the substituents at C_3 and C_4 could not unequivocally be determined by ^1H NMR because of overlapping resonances of H_3, H_4, and benzylic protons. The 3,4-trans geometry and the (3*R*,4*R*) absolute configuration in lactones **11** is evident from (i) related tandem additions of lithiotris(methylthio)methane to **5a** and confirmation of the absolute configuration of the product via conversion to (2*R*,3*R*)-2,3-dimethylbutanediol,[2a] (ii) extensive NMR and X-ray stereochemical analyses of related conjugate addition and aldol products of **5a**,[33] and (iii) confirmation of the absolute configuration by comparison of specific rotations of the obtained lignans with optical rotations of natural lignans of known absolute configuration (vide infra).

Starting from the enantiomer 5(*S*)-(*d*-menthyloxy)-2(5*H*)-furanone **5b** again the all-trans addition products are formed having the (3*S*,4*S*)-configuration. A typical example is the diastereoselective formation of (−)-eudesmin precursor **26**, as shown in Scheme 7 (vide infra).

Synthesis of (−)-Enterolactone, (−)-Hinokinin, (−)-Pluviatolide, and (−)-Enterodiol

Reductive desulfurizations of the addition products **11** to the 3,4-dibenzylated lactones **20** were initially performed with Raney nickel,[39] but its preparation is tedious

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(36) It should be noted that after purification by chromatography, the addition products **11** still contained a small amount of an impurity (<10%) which could be detected by ^1H NMR. We were not able to remove this byproduct at this stage by chromatographic methods. The byproduct can however be effectively removed after the desulfurization and reduction steps as depicted in Scheme 6.

(37) ^1H NMR of the crude product indicated single isomers, the main byproduct from the reaction is the monoalkylated furanone. In this case only the Michael addition took place and the resulting lactone enolate anion has not been quenched by the benzyl bromide.

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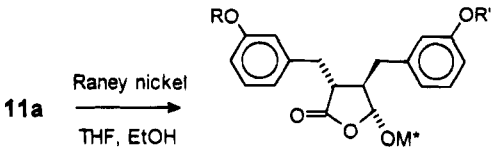
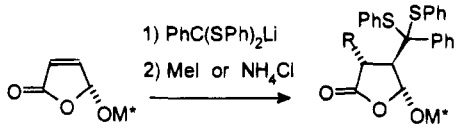
Scheme 4

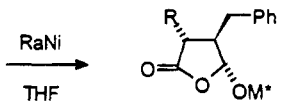


12 R = R'= CH_2Ph
13 R= H , R'= CH_2Ph
14 R= CH_2Ph , R'= H
15 R = R'= H

Scheme 5



5a **16** R = H
17 R = Me



18 R = H 71%
19 R = Me 66%

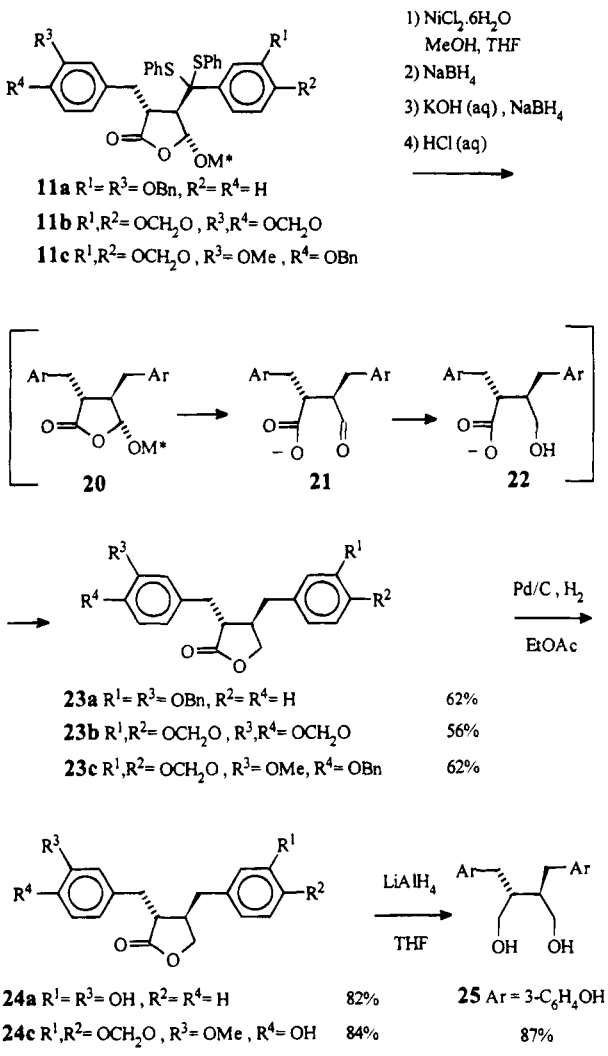
and a large excess of Raney nickel was often required to achieve complete reduction of the thioacetal group.[2,33] For preparative purposes large quantities of Raney nickel are therefore required. Furthermore treatment of the *O*-benzyl-protected substrate **11a** with Raney nickel led to a complex mixture of products **12**–**15**, giving serious purification problems (Scheme 4).

It appears that the yield of the Raney nickel desulfurization reactions strongly depends on the dithiane used, as clean desulfurization was found in the case of some dibenzylated[2,33] and monobenzylated lactones using this procedure. Illustrative is the isolation of lactones **18** and **19** in 71% and 66% overall yield, respectively, after tandem conjugate addition–alkylation or protonation and subsequent Raney nickel reduction of the conjugate addition products **16** and **17** (Scheme 5).

We preferred to use nickel boride for the desulfurization reactions of lactones **11**.[40] To complete the synthesis of 3,4-dibenzyllactone lignan structures from **11**, several steps, including thioacetal desulfurization, acetal hydrolysis with removal of the auxiliary menthol, reduction of an aldehyde group sensitive to epimerization at the α-position, and ring closure of the resulting alcohol to the γ-lactone without affecting the stereocenters at C_3 and C_4, are necessary (Scheme 6). *We devised a one-pot procedure for the conversion of lactones **11** to lactones **23**, which proved to be highly efficient.*

Small scale (1 mmol) desulfurizations of the addition products **11** are best performed using nickel boride generated in situ from 5 equiv of $NiCl_2{\cdot}6H_2O$ and 20 equiv of $NaBH_4$ in MeOH in the presence of the substrate (in the case of **11a** and **11c** some THF is added to improve solubility). The excess of $NiCl_2$ is necessary to achieve complete desulfurization. The reduction of the intermediate **20** (Scheme 6) is carried out in the same pot, simply by adding aqueous KOH and additional $NaBH_4$ to the nickel boride reaction mixture. The function of the KOH is apparently 2-fold: (i) it reduces the catalytic activity of the nickel boride and therefore the additional $NaBH_4$ is not immediately decomposed to H_2 and boric acid (it should be noted that if an equimolar amount of KOH, compared to $NiCl_2$, is used no acetal reduction takes place) and (ii) it opens the lactone **20** to the aldehyde derative **21**, which is reduced by $NaBH_4$ to the alcohol **22**. Subsequent ring closure of **22** is effected by acidification with aqueous HCl to give dibenzylbutyrolactones **23a**, **23b**, and **23c** in satisfactory overall yields and in enantiomerically pure form. Using this one-pot procedure the dibenzylbutyrolactone lignan (−)-hinokinin (**23b**) ($[\alpha]^{23}_D$ −36.0 (*c* 1.00, $CHCl_3$); lit.[41] −34.0, lit.[15] −34.7) was obtained in 37% overall yield from 5-(*l*-menthyloxy)-2(5*H*)-furanone **5a**. The benzyl-protected lactones **23a** and **23c** were readily deprotected with H_2 on Pd/C to provide the enantiomerically pure lignan (−)-enterolactone (**24a**) ($[\alpha]^{23}_D$ −43 (*c* 0.29, $CHCl_3$); lit.[20] −38.4, lit.[42] −40.5) and the natural lignan (−)-pluviatolide (**24c**) ($[\alpha]^{23}_D$ −30.1 (*c* 0.93, $CHCl_3$); lit.[43] −35.5).[44] Furthermore reduction of enterolactone **24a** with $LiAlH_4$

Scheme 6



11a R^1= R^3= OBn, R^2= R^4= H
11b R^1,R^2= OCH_2O , R^3,R^4= OCH_2O
11c R^1,R^2= OCH_2O , R^3= OMe , R^4= OBn

23a R^1= R^3= OBn, R^2= R^4= H 62%
23b R^1,R^2= OCH_2O , R^3,R^4= OCH_2O 56%
23c R^1,R^2= OCH_2O , R^3= OMe, R^4= OBn 62%

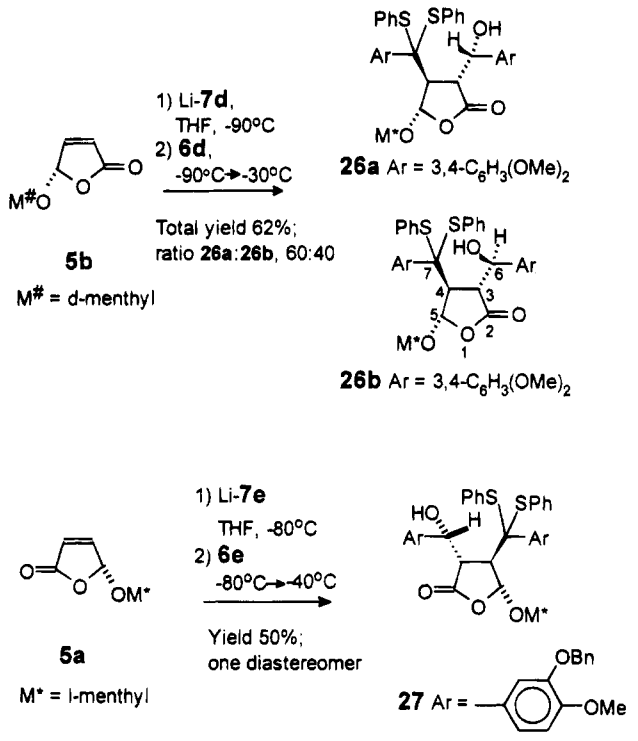
24a R^1= R^3= OH , R^2= R^4= H 82%
24c R^1,R^2= OCH_2O , R^3= OMe , R^4= OH 84%

25 Ar = 3-C_6H_4OH 87%

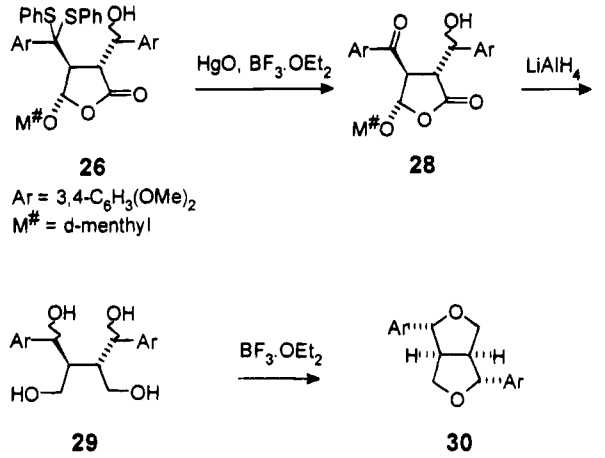
(40) (a) Back, T. G.; Yang, K.; Krouse, H. R. *J. Org. Chem.* **1992**, *57*, 1986. (b) Ganem, B.; Osby, J. O. *Chem. Rev.* **1986**, *86*, 763.

(41) Haworth, R. D.; Woodcock, D. *J. Chem. Soc.* **1938**, 1985.
(42) Yoda, H.; Kitayama, H.; Katagiri, T.; Takabe, K. *Tetrahedron* **1992**, *48*, 3313.

Scheme 7



Scheme 8



gave the enantiomerically pure lignan (−)-enterodiol[12,45] (**25**) (87% yield, $[\alpha]^{23}_D$ −13.2 (*c* 1.0, EtOH)).

It should be emphasized that according to ^{1}H NMR no trace of epimers of **23a**−**c** and **24a**,**c** was found. This means that for partial racemization, epimerization both at C_3 and C_4 in the dibenzylated lactones must have occurred which is highly unlikely. In addition optical rotations compared well with reported values of lignans obtained from natural sources or via different synthetic routes and indicate enantiomerically pure products.

It should be emphasized that besides the easy access to butyrolactones bearing identical C_3 and C_4 benzyl substituents, the method presented here allows facile introduction of two distinctly substituted benzyl moieties as is illustrated in the synthesis of (−)-pluviatolide (**24c**).

Synthesis of (−)-Eudesmin (30)

For the synthesis of (−)-eudesmin (**30**) we started with 5(*S*)-(*d*-menthyloxy)-2(5*H*)-furanone (**5b**) as shown in Scheme 7. Conjugate addition of lithiated dithioacetal **7d** to **5b** followed by an aldol condensation of the resulting lactone enolate anion with 3,4-dimethoxybenzaldehyde (**6d**) at −90 °C provided lactone **26** in 62% yield. Much to our surprise two diastereoisomers of **26** were obtained in a 60:40 ratio. Extensive NMR studies (^{1}H NMR, COSY, and NOESY) and conversion of **26** into (−)-eudesmin (**30**) (Scheme 8) unambiguously showed that the lithiated dithiane added trans with respect to the menthyloxy substituent in **5b** and that the addition of the enolate to **6d** occurred exclusively trans with respect to the dithiane substituent. It appeared that the diastereoisomers **26a** and **26b** are epimeric at the secondary carbinol stereocenter C_6, indicating low selectivity in the aldol step.

The stereochemical assignment of **26a** and **26b** is based on NOESY NMR data and molecular modeling; the NOE effects of the proton at the carbinol stereogenic center are very distinctive in this respect.[2b,33] The stereochemical result of the aldol step is in contrast with our previous findings[46] (see also ref 33). Similar observations of low diastereoselectivity in the quenching of lactone enolates with aryl aldehydes have been made by Fujimoto and co-workers[47] in the synthesis of racemic pinoresinol and in aldol reactions of lactone enolates lacking a C_4 substituent.[33] In a related reaction, only different in the substitution pattern of the aromatic groups, we found complete selectivity in the aldol step. Thus addition of the lithiated dithiane **7e** to **5a** was followed by an aldol reaction with aldehyde **6e**. The tandem addition quenching product **27** was isolated in 50% yield (Scheme 7). No epimer could be detected by means of ^{1}H or ^{13}C NMR. The origin of the large difference in selectivity due to an apparently small substituent effect in the aromatic aldehyde remains obscure at present. The dioxabicyclo[3.3.0]octane lignan (−)-eudesmin (**30**) was synthesized from adduct **26** in three steps as outlined in Scheme 8. The low diastereoselectivity at the exocyclic benzylic stereogenic center in the synthesis of **26** (Scheme 7) causes no problems in the preparation of (−)-**30** since both diastereomers are converted to (−)-eudesmin. The integrity of the C_3,C_4 stereocenters in **26** is retained throughout the synthetic route toward **30** and the absolute configuration at these centers is decisive for the absolute configuration at the benzylic positions of **30**.

Dithiane **26** was first converted into ketone **28** in 89% yield using HgO in combination with BF_3·OEt_2. Subsequent multistep reduction of **28** with 4 equiv of $LiAlH_4$ afforded tetrol **29** in 67% yield. The formation of **29** from **28** involves a ketone and an ester reduction, ring opening and formation of a hemiacetal, which is supposed to be in equilibrium with the aldehyde and *d*-menthol, and finally reduction of the aldehyde moiety to the alcohol.

(43) (a) Corrie, J. E. T.; Green, G. H.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1970**, *23*, 233. (b) Ganeshpure, P. A.; Stevenson, R. *Aust. J. Chem.* **1982**, *35*, 2175.

(44) Especially the phenolic lignans show a large concentration, temperature, and solvent dependency for the specific rotation.

(45) (a) Cooley, G.; Farrant, R. D.; Kirk, D. N.; Wynn, S. *Tetrahedron Lett.* **1981**, *22*, 349. (b) Asaoka, M.; Fujii, N.; Shima, K.; Takei, H. *Chem. Lett.* **1988**, 805. (c) Cooley, G.; Farrant, R. D.; Kirk, D. N.; Patel, S.; Wynn, S.; Buckingham, M. J.; Hawkes, G. E.; Hursthouse, M. B.; Galas, A. M. R.; Lawson, A. M.; Setchell, D. R. *J. Chem. Soc., Perkin Trans. II* **1984**, 489. (d) The only example of enantiomerically pure (*R*,*R*)-(−)-enterodiol was reported by Groen, M. B. Eur. Pat. Appl. EP 43150; *Chem. Abstr.* **1980**, *96*, P162321q.

(46) Jansen, J. F. G. A. Ph.D. Thesis, University of Groningen, 1991.

(47) Fujimoto, H.; Nakatsubo, F.; Higuchi, T. *Mokuzoi Gakkaishi* **1982**, *28*, 555; *Chem. Abstr.* **1982**, *98*, 71774q.

^1H and ^{13}C NMR spectra of **29** indicated the presence of three different stereoisomers of the tetrol **29** due to low selectivity in the reduction steps resulting in epimers at the benzylic stereocenters. As the stereochemical integrity at the crucial C_3 and C_4 stereogenic centers (lactone numbering) is not affected, this mixture of stereoisomers could be used in the final ring closure step. The formation of the dioxabicyclo[3.3.0]octane structure was completed by dehydration of **29** using $BF_3{\cdot}OEt_2$, according to a method described by Fujimoto and co-workers.[46]

Enantiomerically pure (−)-eudesmin (**30**) (mp 106−108 °C, lit.[48] mp 107−109 °C) was obtained in 16% overall yield in four steps from 5(*S*)-(*d*-menthyloxy)-2(5*H*)-furanone (**5b**). ^1H and ^{13}C NMR data were in agreement with those reported for racemic eudesmin[49] whereas an identical rotation ($[\alpha]^{20}_D$ −64.2 (*c* 1.1, $CHCl_3$)) and mass spectrum were obtained for the synthetic optically pure (−)-**30** and the natural product. The absolute configuration (1*S*,2*R*,5*S*,6*R*) of synthetic (−)-eudesmin (**30**) is based upon the absolute configuration[50] of butenolide **5b** and the all-trans stereoselectivity in the tandem conjugate addition aldol reaction giving Michael adduct **26**.

Conclusions

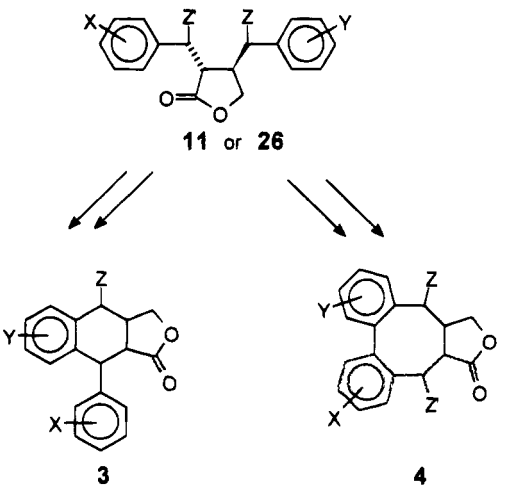
We have shown that 5-(menthyloxy)-2(5*H*)-furanones **5a** and **5b** are excellent chiral synthons for the preparation of dibenzylbutyrolactone and dioxabicyclo[3.3.0]-octane lignans via short and completely diastereoselective routes. The tandem Michael addition−alkylation (or aldol) procedures allow easy variation in benzyl substituents, give complete stereocontrol at the essential stereogenic centers, and allow assembly of the lignan structural framework in enantiomerically pure form in a single step.[51] The enantiomerically pure dibenzylbutyrolactones **11**, **26**, and **27** are also excellent precursors for the synthesis of dibenzocyclooctadiene-type lignans **4** and aryltetralin lignans **3** (Scheme 9).

Oxidative coupling of dibenzyltetrahydrofurans to type **4** lignans is well documented,[14,52] whereas Vandewalle and co-workers[53] used the 5-(menthyloxy)butenolide approach in an elegant route to podophyllotoxin and analogues **3**. The flexibility with respect to hydroxy (and keto groups) at the benzylic positions in **11**, **26**, and **27**, as described above, is essential to the synthesis of the various structural classes of lignans as depicted in Figure 1.

Experimental Section

General Remarks. Melting points are uncorrected. ^1H NMR data were recorded at 200 or 300 MHz. ^{13}C NMR data were recorded at 50 or 75.5 MHz. $CDCl_3$ was used as solvent unless stated otherwise. Chemical shifts are reported in ppm relative to TMS. Coupling constants *J* are denoted in hertz. IR spectra were recorded neat or as KBr pellet. Microanalyses were performed by the analytical department of the University of Groningen. HRMS mass spectra were recorded on a AEI MS-902 spectrometer. The thioacetalization, bromination, and the tandem addition reactions were performed under an inert nitrogen atmosphere in flame-dried glassware. Flash chromatography was performed using Merck silica gel 60. Solvents were purified using standard procedures. 5-(Menthyloxy)-2(5*H*)-furanones **5** were synthesized according to the procedure previously described.[30] Bis(phenylthio)phenylmethane was prepared according to the procedure of Ager.[54] Benzaldehydes **6** were purchased from Janssen Chimica and used without purification. All other reagents are commercially available and were used without purification unless stated otherwise.

Scheme 9



General Procedure for Thioacetal Formation:[34] 3-(benzyloxy)-1-(bis(phenylthio)methyl)benzene (7a). To a stirred solution of **6a** (10.6 g, 50 mmol) in 100 mL of CH_2Cl_2 was added 12.0 g (109 mmol, 2.2 equiv) of thiophenol followed by 1.3 g of $AlCl_3$ in portions. After stirring for 2 h, the reaction mixture was quenched with 100 mL of water. The resulting mixture was extracted with 3 × 100 mL of CH_2Cl_2. The combined CH_2Cl_2 layers were washed with 3 × 100 mL saturated Na_2CO_3 solution, dried over Na_2SO_4, and concentrated. Pure thioacetal **7a** (16.7g, 81%) was obtained after one crystallization from Et_2O/ hexane as a white-yellow solid: mp 95.8−96.4 °C; ^1H NMR δ 7.42−7.15 (m, 16H), 7.04−6.85 (m, 3H), 5.40 (s, 1H), 5.01 (s, 2H); ^{13}C NMR δ 158.77, 141.15, 136.83, 134.47, 132.55, 129.49, 128.85, 128.58, 128.00, 127.81, 127.57, 120.52, 114.94, 114.03, 69.96, 60.32.

5-(Bis(phenylthio)methyl)-1,3-benzodioxole (7b) was synthesized according to the procedure for the preparation of **7a**. Starting from **6b** (7.5 g, 50 mmol), pure thioacetal **7b** (15.2 g, 90%) was obtained after one crystallization from EtOH: mp 45−47.5 °C (lit.[15] mp 45−47.5 °C); ^1H NMR δ 7.38−7.18 (m, 10H), 6.98 (d, 1H, *J* = 1), 6.78 (dd, 1H, *J* = 1, *J* = 7), 6.62 (d, 1H, *J* = 7), 5.87 (s, 2H), 5.36 (s, 1H); ^{13}C NMR δ 147.59, 147.14, 134.38, 133.29, 132.12, 128.64, 127.54, 121.30, 108.04, 107.66, 101.01, 59.96.

4-(Bis(phenylthio)methyl)-1,2-(dimethoxy)benzene (7d) was synthesized according to the procedure for the preparation of **7a**. Starting from **6d** (8.3 g, 50 mmol), pure **7d** (14.2 g, 80%) was obtained after one crystallization from EtOH/EtOAc: mp 68−69 °C (lit.[15] mp 68−69 °C); ^1H NMR δ 7.40−7.21 (m, 10H), 6.95−6.75 (m, 3H), 5.44 (s, 1H), 3.84 (s, 3H), 3.80 (s, 3H); ^{13}C NMR δ 148.67, 148.54, 134.41, 132.43, 131.88, 128.67, 127.51, 120.10, 110.67, 110.51, 59.97, 55.76.

2-(Benzyloxy)-4-(bis(phenylthio)methyl)-1-methoxybenzene (7e) was synthesized according to the procedure for the preparation of **7a**. Starting from **6e** (10 g, 40 mmol), pure **7e** (16 g, 88%) was obtained after one crystallization from

(48) Kaku, T.; Ri, H. *J. Pharm. Soc. Jpn.* **1937**, *57*, 101; *Chem. Abstr.* **1938**, *32*, 3365.

(49) (a) Pelter, A.; Ward, R. S.; Watson, D. J.; Collins, P.; Kay, I. T. *J. Chem. Soc., Perkin Trans. 1* **1982**, 175. (b) Pelter, A. *J. Chem. Soc. C* **1967**, 1376.

(50) For the assignment of the absolute configuration of a 1,4-addition product to (+)-5(*S*)-(menthyloxy)-2(5*H*)-furanone (**5b**), see ref 33.

(51) A related strategy to prepare optically active lignan precursors based upon the tandem addition quenching reaction to butenolide **5a** was described by Pelter and Ward: Pelter, A.; Ward, R. S.; Martin Jones, D.; Maddocks, P. *Tetrahedron: Asymm.* **1990**, *1*, 857.

(52) (a) Robin, J.-P.; Landais, Y. *Tetrahedron* **1992**, *48*, 819. (b) Pelter, A.; Ward, R.S.; Martin Jones, D.; Maddocks, P. *Tetrahedron: Asymm.* **1992**, *3*, 239. (c) Pelter, A.; Ward, R. S.; Pritchard, M. C. Kay, I. T. *Tetrahedron Lett.* **1985**, *26*, 6377.

(53) van Speybroeck, R.; Guo, H.; van der Eycken, J.; VandewWalle, M. *Tetrahedron* **1991**, *47*, 4675.

(54) Ager, D. J. *J. Chem. Soc., Perkin Trans. I* **1983**, 1131.

CH_2Cl_2/hexane: mp 82.6–82.9 °C; ^1H NMR δ 7.45–7.18 (m, 15H), 6.98 (d, 1H, J = 1.8), 6.90 (dd, 1H, J = 1.8, J = 8.1), 6.71 (d, 1H, J = 8.1), 5.35 (s, 1H), 5.05 (s, 2H), 3.82 (s, 3H); ^{13}C NMR δ 149.21, 147.72, 136.73, 134.32, 132.40, 131.67, 128.61, 128.37, 127.73, 127.53, 127.33, 120.65, 113.41, 111.06, 70.71, 59.76, 55.82.

General Procedure for the Synthesis of Benzylbromides:[35b] **3-(Benzyloxy)-1-(bromomethyl)benzene (9a).** To a stirred solution of **6a** (10.6 g, 50 mmol) in 50 mL of CH_2Cl_2 was added 2.3 g of $NaBH_4$ (62 mmol) in 25 mL of MeOH. After stirring for 1 h, the reaction mixture was poured into 100 mL of water followed by extraction with CH_2Cl_2 (3 × 50 mL), drying (Na_2SO_4), and evaporation of the solvent. The alcohol **8a** obtained in this way was used in the next step without purification. To a stirred solution of **8a** in 100 mL of ether was added dropwise 15.5 g of PBr_3 (57 mmol) in 35 mL of ether. After stirring for 3 h at room temperature, the reaction mixture was poured in 100 mL of water, followed by extraction with CH_2Cl_2 (3 × 75 mL), drying of the organic layer (Na_2SO_4), and evaporation of the solvent. After crystallization of the residue from n-hexane, pure **9a** (11.2 g, 80%) was obtained: mp 51–53 °C (lit.[35] mp 55 °C); ^1H NMR δ 7.47–7.26 (m, 5H), 7.06–6.93 (m, 4H), 5.10 (s, 2H), 4.50 (s, 2H); ^{13}C NMR δ 159.02, 139.26, 136.80, 129.93, 128.69, 128.12, 127.60, 121.65, 115.53, 115.02, 70.07, 33.60.

5-(Bromomethyl)-1,3-benzodioxole (9b) was synthesized according to the procedure for the preparation of **9a.** Starting from **6b** (7.5 g, 50 mmol), pure **9b** (7.8 g, 73%) was obtained after crystallization from n-hexane: mp 45.6–47.2 °C (lit.[55] 49–50 °C); ^1H NMR δ 6.78 (s, 1H), 6.73 (d, 2H, J = 7), 6.48 (d, 1H, J = 7), 5.92 (s, 2H), 4.46 (s, 2H); ^{13}C NMR δ 147.47, 147.61, 122.55, 109.28, 108.12, 101.16, 24.09.

1-(Benzyloxy)-4-(bromomethyl)-2-methoxybenzene (9c) was synthesized according to the procedure for the preparation of **9a**. Starting from **6c** (12.1 g, 50 mmol), pure **9c** (13.0 g, 84%) was obtained after one crystallization from hexane/Et_2O: mp 69.8–73.4 °C (lit.[42b] mp 70–72 °C, lit.[35b] mp 73 °C); ^1H NMR δ 7.46–7.27 (m, 5H), 6.96–6.81 (m, 3H), 5.17 (s, 2H), 4.50 (s, 2H), 3.92 (s, 3H); ^{13}C NMR δ 149.68, 148.38, 136.86, 130.68, 128.58, 127.91, 127.22, 121.49, 113.71, 112.59, 70.93, 56.03, 34.38.

4-(Bromomethyl)-1,2-dimethoxybenzene (9d) was synthesized according to the procedure for the preparation of **9a**. Starting from **6d** (9.9 g, 60 mmol), pure **9d** (11.2 g, 81%) was obtained after one crystallization from n-hexane: ^1H NMR δ 6.97–6.88 (m, 2H), 6.79 (m, 1H), 4.48 (s, 2H), 3.90 (s, 3H), 3.86 (s, 3H); ^{13}C NMR δ 149.00, 148.85, 130.02, 121.35, 111.86, 110.82, 55.73, 34.24.

(3*R*,4*R*,5*R*)-3-[(3-(Benzyloxy)phenyl)methyl]-4-[(3-(benzyloxy)phenyl)bis(phenylthio)methyl]-5-(*l*-menthyloxy)-dihydro-2(3*H*)-furanone (11a). To a stirred solution of **7a** (4.14 g, 10 mmol) in 50 mL of THF was added at −20 °C 6.7 mL of n-BuLi in hexanes (1.6 N, 10.7 mmol), resulting in a dark red solution. This solution was stirred at −20 °C for 90 min and subsequently cooled to −85 °C. A solution of **5a** (2.38 g, 10 mmol) in 30 mL of THF was added dropwise, keeping the temperature below −80 °C. The reaction mixture was stirred at −80 °C for 2 h and 1.29 mL of TMEDA was added, immediately followed by **9a** (3.10 g, 11 mmol). The mixture was allowed to warm slowly to −20 °C, and stirred at this temperature for 16 h, poured into 300 mL of water, and extracted with 3 × 100 mL of CH_2Cl_2. The combined organic layers were washed with saturated NH_4Cl (2 × 50 mL) and water (50 mL) and dried (Na_2SO_4). The solvent was evaporated and the resulting crude product (9.82 g) was purified by flash chromatography (silica gel, CH_2Cl_2/n-hexane 1:1) after which **11a** (5.71 g, 67%) was obtained as a very viscous yellow oil, which partly solidified upon standing: $[\alpha]^{23}_D$ −125 (c 1.02, $CHCl_3$) IR (KBr) 1776 (C=O); ^1H NMR δ 7.43–7.03 (m, 24H), 6.90–6.64 (m, 4H), 5.86 (s, 1H), 4.98 (s, 2H), 4.93 (s, 2H), 3.47 (dt, 1H J = 10.7, J = 3.8), 3.45–3.34 (m, 1H), 3.05–2.95 (m, 3H), 2.03–1.88 (m, 2H), 1.69–1.59 (m, 2H), 1.40–1.18 (m, 2H), 1.02–0.68 (m, 3H), 0.88 (d, 3H, J = 6.0), 0.86 (d, 3H, J = 7.0), 0.69 (d, 3H, J = 6.8); ^{13}C NMR δ 177.40, 158.86, 158.51, 139.66, 139.03, 137.06, 136.74, 135.85, 135.76, 132.81, 132.59, 132.52, 132.38, 130.52, 129.35, 129.22, 129.06, 128.81, 128.59, 128.52, 128.46, 128.40, 128.17, 128.02, 127.86, 127.73, 127.48, 122.43, 121.67, 121.35, 121.03, 116.05, 115.93, 114.94, 114.66, 114.31, 113.35, 100.25, 76.77, 70.83, 69.91, 69.78, 54.96, 47.89, 45.41, 39.13, 38.18, 34.31, 31.32, 25.29, 22.72, 22.78, 21.10, 15.23; HRMS $M^+ - 2 \times C_6H_5S$ = 848 − 218 = 630, calcd 630.335, found 630.335.

(3*R*,4*R*,5*R*)-3-(1,3-Benzodioxol-5-ylmethyl)-4-[(1,3-benzodioxol-5-yl)bis(phenylthio)methyl]-5-(*l*-menthyloxy)-dihydro-2(3*H*)-furanone (11b) was synthesized according to the procedure for the preparation of **11a**. After chromatography (silica gel, hexane/ EtOAc 6:1), **11b** (4.83 g, 66%) was obtained as a gum which solidified upon standing: $[\alpha]^{23}_D$ −157 (c 1.04, $CHCl_3$); IR (KBr) 1776 cm^{-1} (C=O); ^1H NMR δ 7.4–7.0 (m, 12H), 6.62–6.48 (m, 4H), 5.97–5.84 (m, 4H), 5.80 (s, 1H), 3.43 (dt, 1H, J = 4.3, J = 10.6), 3.24–3.19 (m, 1H), 3.02–2.80 (m, 3H), 2.10–1.92 (m, 2H), 1.71–1.54 (m, 2H), 1.40–1.19 (m, 2H), 1.05–0.74 (m, 3H), 0.93 (d, 3H, J = 6.6), 0.89 (d, 3H, J = 7.3), 0.72 (d, 3H, J = 7.0); ^{13}C NMR δ 177.14, 147.69, 147.41, 147.14, 146.16, 136.58, 132.34, 130.99, 130.98, 130.41, 129.16, 128.34, 128.25, 122.69, 122.42, 109.90, 109.17, 108.01, 107.43, 101.30, 100.66, 100.14, 76.76, 70.78, 54.81, 47.76, 45.50, 39.09, 37.69, 34.24, 31.25, 25.27, 22.61, 22.22, 20.96, 15.10; HRMS $M^+ - 2 \times C_6H_5S$ = 724 − 218 = 506, calcd 506.230, found 506.230. Anal. Calcd for $C_{42}H_{44}O_7S_2$: C, 69.61; H, 6.08; S, 8.84. Found: C, 69.75; H, 6.37; S, 8.39.

(3*R*,4*R*,5*R*)4-[1,3-Benzodioxol-5-ylbis(phenylthio)methyl]-3-[4-(benzyloxy)-3-methoxyphenyl)methyl]-5-(*l*-menthyloxy)dihydro-2(3*H*)-furanone (11c) was synthesized according to the procedure for the preparation of **11a**. Starting from **7b** (1.7 g, 5.2 mmol), **5a** (1.19 g, 5.0 mmol), and **9c** (1.7 g, 5.5 mmol), pure **11c** (2.42 g, 59%) was obtained after chromatography (silica gel, hexane/EtOAc 5:1) as a slightly yellow gum which solidified upon standing: $[\alpha]^{23}_D$ −130 (c 0.80, $CHCl_3$); IR (KBr) 1776 cm^{-1} (C=O); ^1H NMR δ 7.43–7.14 (m, 12H), 7.06–7.01 (dd, 1H, J = 8.1 J = 1.7), 6.70–6.59 (m, 2H), 6.48 (d, 2H, J = 8.1), 5.97 (s, 1H), 5.95 (d, 1H, J = 0.9), 5.84 (s, 1H), 5.13 (s, 2H), 3.82 (s, 3H), 3.48 (dt, 1H, J = 3.9, J = 10.7), 3.26–3.19 (m, 1H), 3.11–2.80 (m, 3H), 2.12–1.98 (m, 2H), 1.70–1.63 (m, 2H), 1.43–1.23 (m, 2H), 1.03–0.61 (m, 3H), 0.95 (d, 3H, J = 6.8), 0.91 (d, 3H, J = 6.8), 0.75 (d, 3H, J = 6.8); ^{13}C NMR δ 177.6, 149.5, 147.9, 147.3, 147.1, 137.3, 136.7, 132.6, 132.5, 131.7, 130.5, 129.2, 128.5, 128.3, 127.7, 127.6, 127.1, 122.5, 121.8, 113.7, 113.1, 109.3, 107.4, 101.5, 100.3, 76.8, 71.0, 70.8, 55.8, 55.0, 47.9, 45.6, 39.2, 37.8, 34.3, 34.3, 31.3, 25.5, 22.7, 22.3, 21.1, 15.2; HRMS $M^+ - 2 \times C_6H_5S$ = 716 − 218 = 598. calcd 598.293, found 598.293. Anal. Calcd for $C_{49}H_{52}O_7S_2$: C, 72.05; H, 6.37; S, 7.84. Found: C, 71.74; H, 6.38; S, 7.19.

(3*R*,4*R*,5*R*)3-[(3,4-Dimethoxyphenyl)methyl]-4-[(3,4-dimethoxyphenyl)bis(phenylthio)methyl]-5-(*l*-menthyloxy)dihydro-2(3*H*)-furanone (11d) was synthesized according to the procedure for the preparation of **11a**. Starting from **7d** (1.84 g, 5 mmol), **5a** (1.19 g, 5 mmol), and **9d** (1.16 g, 5 mmol), pure **11d** (1.87 g, 50%) was obtained after chromatography (silica gel, Et_2O/hexane 1:1) as a viscous oil: $[\alpha]^{23}_D$ −148 (c 1.03, $CHCl_3$); ^1H NMR δ 7.35–7.11 (m, 12H), 6.98–6.95 (m, 1H), 6.69–6.54 (m, 3H), 5.74 (s, 1H), 3.82 (s, 6H), 3.77 (s, 3H), 3.65 (s, 3H), 3.46–3.30 (m, 2H), 3.08–2.90 (m, 3H), 2.03–1.89 (m, 2H), 1.67–1.59 (m, 2H), 1.40–1.18 (m, 2H), 1.02–0.68 (m, 3H), 0.88 (d, 3H, J = 6.6), 0.86 (d, 3H, J = 7.3), 0.69 (d, 3H, J = 7.0); ^{13}C NMR δ ($CDCl_3$, 75 MHz) 177.14, 148.45, 148.33, 147.87, 147.44, 136.76, 132.70, 132.37, 130.35, 130.08, 129.53, 128.86, 128.19, 128.06, 127.16, 121.50, 120.49, 112.59, 112.47, 110.54, 109.75, 99.83, 76.30, 70.87, 55.42, 47.64, 45.35, 38.76, 37.38, 34.03, 31.01, 25.08, 22.43, 22.03, 20.72, 14.95.

(4*R*,5*R*)-4-(Phenylmethyl)-5-(*l*-menthyloxy)dihydro-2(3*H*)-furanone (18). To a solution of [bis(phenylthio)methyl]-benzene (1.54 g, 5 mmol) in 30 mL of THF was added at −90 °C 3.8 mL of n-BuLi in hexanes (1.6 N, 5.9 mmol). The mixture was stirred at −90 °C for 1 h and subsequently a solution of **5a** (1.19 g, 5 mmol) in 40 mL of THF was added dropwise during 30 min and stirring at −90 °C was continued

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for 90 min. The reaction mixture was poured into 200 mL of saturated aqueous NH_4Cl and extracted with Et_2O (3 × 100 mL). The organic layers were dried over Na_2SO_4 and concentrated. The intermediate **16** was dissolved in 40 mL of THF and 5 teaspoons of Raney nickel were added. The mixture was stirred at room temperature for 16 h and the supernatant liquid was decanted from the solid material. The solids were extracted four times with Et_2O and the combined organic extracts were dried over Na_2SO_4 and concentrated. The crude product **18** was purified by chromatography (silica gel, CH_2Cl_2) to give pure **18** (1.17 g, 71%) as an oil: $[\alpha]^{23}_D$ −96.9 (*c* 0.30, CH_2Cl_2); IR (neat) 1770, 720, 690 cm^{-1}; ^1H NMR δ 7.53−6.79 (m, 5H), 5.33 (d, 1H, *J* = 1.4), 3.62−0.60 (m, 24H); ^{13}C NMR δ 175.66, 141.66, 128.96, 128.51, 127.65, 103.84, 76.86, 47.50, 42.66, 39.44, 37.50, 34.10, 33.07, 31.00, 25.26, 22.90, 21.95, 20.73, 15.48; HRMS calcd 330.219, found 330.218.

(3*R*,4*R*,5*R*)-3-Methyl-4-(phenylmethyl)-5-(*l*-menthyloxy)-dihydro-2(3*H*)-furanone (19). To a solution of [bis(phenylthio)methyl]benzene (1.54 g, 5 mmol) in 30 mL of THF was added at −90 °C a solution of *n*-BuLi in hexanes (1.6 N, 5.9 mmol). The mixture was stirred at −90 °C for 1 h and subsequently a solution of **5a** (1.19 g, 5 mmol) in 30 mL of THF was added during 15 min and the mixture was stirred at −80 °C for 90 min. Then 5 mL of MeI was added via syringe and the mixture was allowed to warm to −50 °C and stirred at this temperature for 2 h. Then the reaction mixture was poured into 200 mL of saturated aqueous NH_4Cl and extracted with Et_2O (3 × 100 mL). The organic layers were dried over Na_2SO_4 and concentrated; 1 g of the crude product was dissolved in 40 mL of THF and 5 teaspoons of Raney nickel were added. Stirring at room remperature was continued for 16 h and the solvent was decanted. The solids were extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed with water, dried over Na_2SO_4, and concentrated to give 0.47 g of a white solid. Crystallization from petroleum ether (40−60 °C) at −18 °C gave pure **19** (0.40 g, 66%) as a white solid: mp 94.5 −95 °C; $[\alpha]^{23}_D$ −112.9 (*c* 1.0, $CHCl_3$); IR (Nujol) 1791 cm^{-1}; ^1H NMR δ 7.2 (m, 5H), 5.3 (d, 1H, *J* = 4.0), 3.4 (m, 1H), 2.8 (m, 1H), 2.2 (m, 3H), 1.8 (m, 1H), 1.6 (m, 2H), 1.2 (m, 3H), 1.1 (d, 3H, *J* = 6.8), 0.8 (m, 12H); ^{13}C NMR δ 177.92, 137.42, 128.84, 128.45, 126.56, 103.19, 77.75, 49.91, 47.48, 40.43, 39.59, 36.93, 34.03, 31.09, 25.10, 22.72, 22.01, 20.75, 15.51, 15.36; HRMS calcd 344.235, found 344.235. Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.30; H, 9.45.

(3*R*,4*R*)-3,4-Bis[(3-(benzyloxy)phenyl)methyl]dihydro-2(3*H*)-furanone (23a). A stirred solution of **11a** (0.85 g, 1.0 mmol) and $NiCl_2{\cdot}6H_2O$ (1.15 g, 5 mmol) in 5 mL of THF and 50 mL of CH_3OH was cooled to 0 °C. $NaBH_4$ (0.76 g, 20 mmol) was added in small portions in about 20 min at such a rate that the temperature was kept below 10 °C. Immediately after the last portion of $NaBH_4$ was added, 10 mL of a 2 N aqueous solution of KOH (20 mmol) was added at once, followed by additional $NaBH_4$ (0.19 g, 5 mmol), and the mixture was allowed to warm to room temperature while being stirred for 2 h. The black precipitate was filtered off over Celite and the filtrate was acidified with 2 N HCl to pH = 1. Subsequently methanol and THF were removed in vacuo. To the remaining suspension was added 20 mL of water, and the water layer was extracted with 3 × 30 mL of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give 0.81 g of a viscous yellow oil. Menthol was removed by bulb-to-bulb distillation (0.1 mmHg/100 °C) and the remaining oil was purified by chromatography (silica gel, CH_2Cl_2) to give pure **23a** (0.263 g, 62%) as a colorless viscous oil: $[\alpha]^{23}_D$ −22 (*c* 0.90, $CHCl_3$); ^1H NMR δ 7.40−7.15 (m, 12H), 6.93−6.76 (m, 4H), 6.62−6.59 (m, 2H), 5.04 (s, 2H), 5.02 (s, 2H), 4.07 (dd, 1H, *J* = 9.0, *J* = 6.4), 3.83 (dd, 1H, *J* = 9.0, *J* = 7.3), 3.07 (dd, 1H, *J* = 4.7, *J* = 13.7), 2.90 (dd, 1H, *J* = 6.8, *J* = 14.1), 2.65−2.38 (m, 4H); ^{13}C NMR δ 178.3, 159.0, 139.6, 139.3, 136.9, 136.8, 129.7, 128.6, 128.5, 128.0, 127.9, 127.5, 121.9, 121.2, 115.7, 115.4, 113.4, 112.9, 71.1, 69.9, 46.3, 41.2, 38.5, 35.1; HRMS calcd 478.214, found 478.214. Anal. Calcd for $C_{32}H_{30}O_4$: C, 80.30; H, 6.27. Found: C, 79.76; H, 6.19.

(3*R*,4*R*) 3,4-Bis(1,3-benzodioxol-5-ylmethyl)dihydro-2(3*H*)-furanone ((−)-hinokinin, 23b) was prepared following the same procedure as for **23a**. Starting from **11b** (0.24 g, 0.3 mmol), pure **23b** (65 mg, 56%) was obtained as a colorless viscous oil: $[\alpha]^{23}_D$ −36 (*c* 1.00, $CHCl_3$) (lit.[16] $[\alpha]^{23}_D$ −34.7 (*c* 0.7, $CHCl_3$)). Spectral data were identical to those reported in the literature.[16]

(3*R*,4*R*)-4-(1,3-Benzodioxol-5-ylmethyl)-3-[(4-(benzyloxy)-3-methoxyphenyl)methyl]dihydro-2(3*H*)-furanone (23c) was synthesized following the same procedure as for compound **23a**. Starting from **11c** (0.816 g, 1 mmol), **23c** (0.276 g, 62%) was obtained after purification by chromatography (silica gel, CH_2Cl_2) as a colorless oil: $[\alpha]^{23}_D$ −24.5 (*c* 1.08, $CHCl_3$); ^1H NMR δ 7.47−7.29 (m, 5H), 6.84−6.60 (m, 4H), 6.49−6.43 (m, 2H), 5.94 (dd, 2H, *J* = 3.4, *J* = 1.3), 5.14 (s, 2H), 4.16−4.06 (m, 1H), 3.86−3.79 (m, 1H), 3.85 (s, 3H), 2.99 (dd, 1H, *J* = 4.7, *J* = 4.1), 2.85 (dd, 1H, *J* = 6.8, *J* = 4.1), 2.56−2.41 (m, 4H); ^{13}C NMR δ 178.6, 149.8, 147.8, 147.1, 146.3, 137.1, 131.7, 130.8, 128.5, 127.8, 127.3, 121.5, 121.3, 114.1, 112.7, 108.8, 108.2, 101.0, 71.1, 71.0, 55.9, 46.4, 41.1, 38.2, 34.7; HRMS calcd 446.173, found 446.173.

(3*R*,4*R*)-3,4-Bis[(3-hydroxyphenyl)methyl]dihydro-2(3*H*)-furanone ((−)-Enterolactone, 24a). To a solution of **23a** (120 mg, 0.25 mmol) in 20 mL of EtOAc was added 50 mg of 5% Pd on carbon. The flask was charged with a balloon filled with H_2 gas and stirred at room temperature for 16 h. The Pd/C was filtered off over Celite and the the filtrate was concentrated to give 67 mg of a colorless gum. This was crystallized from $CHCl_3$ to give **24a** (61 mg, 82%) as slightly brown crystals: mp 132−134 °C; $[\alpha]^{23}_D$ −43 (*c* 0.29, $CHCl_3$) (lit.[20] 127−129 °C, $[\alpha]^{20}_D$ −38.4 (*c* 0.5, $CHCl_3$); lit.[44b] gum $[\alpha]^{19}_D$ −40.3 (*c* 0.553, $CHCl_3$)). Spectral data were identical to those reported in the literature.[12]

(3*R*,4*R*)-4-(1,3-Benzodioxol-5-ylmethyl)-3-[(4-hydroxy-3-methoxyphenyl)methyl]dihydro-2(3*H*)-furanone ((−)-pluviatolide, 24c) was synthesized according to the procedure described for racemic **24c**.[44] Starting from **23c** (103 mg, 0.23 mmol), pure **24c** (69 mg, 84%) was obtained as a gum, which was crystallized from Et_2O to give a white powder: mp 158−159 °C (lit.[42a] mp 160 °C); $[\alpha]^{23}_D$ −30.1 (*c* 0.93, $CHCl_3$) (lit.[42a] [α] −35); ^1H NMR δ 6.86−6.82 (m, 1H), 6.72−6.60 (m, 3H), 6.48−6.45 (m, 2H), 5.93 (s, 2H), 5.65 (bs, 1H), 4.16−4.08 (m, 1H), 3.90−3.82 (m, 1H), 3.85 (s, 3H), 3.02−2.82 (m, 2H), 2.63−2.43 (m, 4H); ^{13}C NMR δ 178.76, 147.82, 146.69, 146.28, 144.52, 131.62, 129.43, 122.04, 121.54, 114.29, 111.57, 108.80, 108.28, 101.02, 71.21, 55.88, 46.57, 41.00, 38.24, 34.60; HRMS calcd 356.126, found 356.126.

(3*R*,4*R*)-2,3-Bis[(3-hydroxyphenyl)methyl]-1,4-butanediol ((−)-enterodiol, 25) was synthesized from **23a** according to a literature procedure for racemic [^2H]-labeled **25**.[12] Starting from **23a** (69 mg, 0.23 mmol), pure **25** (61 mg, 87%) was obtained as a gum: $[\alpha]^{23}_D$ −13.2 (*c* 1.0, EtOH).[45] Spectral data were identical to those of racemic **25**.[12]

(3*R*,4*S*,5*S*,7α*RS*)-3-[(3,4-Dimethoxyphenyl)hydroxymethyl]-4-[(3,4-dimethoxyphenyl)bis(phenylthio)methyl]-5-(*d*-menthyloxy)dihydro-2(3*H*)-furanone (26). To a stirred solution of **7d** (3.68 g, 10 mmol) in 30 mL of THF was added at −40 °C 6.9 mL of *n*-BuLi in hexanes (1.5 N, 10.3 mmol) followed by stirring for 1 h at −20 °C. An intense dark red anion was formed in this period (anion formation was immediately observed). Subsequently the reaction mixture was cooled to −90 °C before **5b** (2.38 g, 10 mmol) in 40 mL of THF was added during 30 min and the reaction mixture was stirred for 3 h at −90 °C. During this period the color became yellow-orange. Aldehyde **6d** (1.66 g, 10 mmol) was added and the mixture was stirred for 16 h at −30 °C. Quenching of the reaction mixture with 200 mL of saturated aqueous NH_4Cl was followed by extraction with Et_2O (3 × 100 mL), drying of the organic layers (Na_2SO_4), and evaporation of the solvent. The crude adduct was purified by chromatography (silica gel, CH_2Cl_2 followed by ether) to afford pure **26** (4.8 g, 62%) as a 60/40 mixture (6*R*/6*S*) of two diastereoisomers: $[\alpha]^{23}_D$ +98.5 (*c* 0.7, $CHCl_3$); IR 3500, 1788 cm^{-1}; ^1H NMR δ **26**α (60%) 7.4−6.5 (m, 16H), 5.63 (s, 1H), 4.92 (t, 1H, *J* = 6), 3.79 (s, 6H), 3.74 (s, 3H), 3.61 (s, 3H), 3.32 (dt, 1H, *J* = 10.4, *J* = 4.2), 3.17 (s, 1H), 2.20 (d, 1H, *J* = 6), 2.00−1.79 (m, 2H), 1.70−1.52 (m, 3H), 1.43−1.05 (m, 2H), 0.98−0.55 (m, 3H), 0.91 (d, 3H, *J* = 6.6), 0.84 (d, 3H, *J* = 7.3), 0.60 (d, 3H, *J* = 6.6); ^{13}C NMR δ

175.80, 148.70, 148.36, 148.21, 1147.81, 136.58, 132.89, 132.43, 132.15, 130.14, 129.83, 128.19, 128.06, 127.94, 118.45, 112.44, 110.21, 109.90, 109.14, 100.08, 77.31, 73.34, 70.87, 55.36, 51.06, 47.70, 47.40, 38.94, 33.81, 30.98, 25.12, 22.28, 21.91, 20.69, 14.80; ^{1}H NMR δ **26**β (40%) 7.4–6.5 (m, 16H), 5.83 (s, 1H), 4.77 (dd, 1H, J = 1.9, J = 8.0), 3.79 (s, 9H), 3.63 (s, 3H), 3.32 (dt, 1H, J = 10.4, J = 4.2), 3.08 (s, 1H), 2.54 (d, 1H, J = 1.9), 2.05–1.80 (m, 2H), 1.70–1.50 (m, 3H), 1.40–1.05 (m, 2H), 0.98–0.55 (m, 3H), 0.87 (d, 3H, J = 6.6), 0.79 (d, 3H, J = 7.3), 0.65 (d, 3H, J = 6.6); ^{13}C NMR δ 175.07, 148.97, 148.48, 148.21, 147.44, 136.46, 132.89, 132.43, 132.15, 130.14, 129.77, 128.34, 128.06, 127.45, 120.62, 112.22, 110.42, 109.54, 109.32, 100.38, 77.49, 73.34, 70.74, 55.36, 52.65, 47.52, 43.61, 39.86, 34.06, 31.10, 24.68, 22.55, 21.79, 20.75, 15.07; HRMS $M^+ - 2 \times C_6H_5S$ = 772 − 218 = 554, calcd 554.288, found 554.287.

(3*S*,4*R*,5*R*,7a*S*)-3-[(3-(Benzyloxy)-4-methoxyphenyl)hydroxymethyl]-4-[(3-(benzyloxy)-4-methoxyphenyl)bis(phenylthio)methyl]-5-(*l*-menthyloxy)dihydro-2(3*H*)-furanone (27) was synthesized according to the procedure for the preparation of **26**. Starting from **7e** (4.44 g, 10 mmol), **5a** (2.38 g, 10 mmol), and **6e** (7.5 g, 30 mmol), pure **27** (4.6 g, 50%) was obtained after triple chromatography (Al_2O_3, CH_2Cl_2) as a viscous oil: $[\alpha]^{23}_D$ −98 (*c* 0.60, $CHCl_3$); ^{1}H NMR δ 7.4–6.85 (m, 24H), 6.60–6.50 (m, 2H), 5.1–4.95 (m, 2H), 5.05–4.90 (m, 2H), 4.93 (bs, 1H), 4.67 (d, 1H, J = 8.4), 3.74 (s, 6H), 3.40 (dt, 1H, J = 3.7, J = 10.6), 3.03 (d, 1H, J = 8.4), 2.75 (s, 1H), 2.14–1.90 (m, 2H), 1.67–1.48 (m, 2H), 1.36–1.12 (m, 2H), 0.98–0.58 (m, 3H), 0.86 (d, 3H, J = 6.6), 0.85 (d, 3H, J = 7.3), 0.69 (d, 3H, J = 6.6); ^{13}C NMR δ 176.98, 149.21, 148.23, 147.38, 136.79, 136.73, 132.0, 133.16, 132.48, 131.81, 130.07, 128.97, 128.36, 128.27, 128.21, 128.12, 127.66, 127.57, 127.20, 127.05, 126.93, 120.82, 120.31, 115.24, 112.22, 110.91, 110.54, 100.65, 76.97, 74.59, 70.92, 70.71, 70.35, 55.78, 55.57, 54.07, 51.11, 47.85, 39.33, 34.08, 31.28, 25.48, 22.52, 22.12, 20.99, 15.01; HRMS $M^+ - C_6H_5S - C_{15}H_{15}O_3$ = 924 − 352 = 572 ($C_{35}H_{40}O_5S$), calcd 572.260, found 572.258.

(3*R*,4*S*,5*S*)-6a*RS*)-3-[(3,4-Dimethoxyphenyl)hydroxymethyl]-4-[(3,4-dimethoxyphenyl)oxomethyl]-5-(*d*-menthyloxy)dihydro-2(3*H*)-furanone (28). To a stirred solution of 2.1 g (2.7 mmol) of the mixture of **26**α and **26**β in 160 mL of wet THF (15% H_2O) was added 2 g (9.2 mmol) of yellow HgO, followed by 2 mL of BF_3·OEt_2 (48% BF_3). After stirring for 1 h, 100 mL of ether was added and the reaction mixture was washed with 2 × 100 mL of saturated Na_2CO_3, 100 mL of water, and 200 mL of brine. Drying (Na_2SO_4) was followed by evaporation of the solvent. The crude adduct was dissolved in 5 mL of $CHCl_3$ (the crystals which are formed are toxic $(PhS)_2Hg$!!) and filtered. Evaporation of the $CHCl_3$ gave 1.36 g (2.4 mmol, 89%) of the pure viscous adduct **28** as a diastereoisomeric mixture (60/40 ratio): $[\alpha]^{23}_D$ +79.4 (*c* 0.8, $CHCl_3$); IR (neat) 3500, 1770 cm^{-1}; ^{1}H NMR δ **28**α (60%) 7.55–6.42 (m, 6H), 5.39 (d, 1H, J = 5.5), 5.30 (d, 1H, J = 2.9), 4.31 (dd, 1H, J = 5.5, J = 9.1), 3.87 (s, 3H), 3.80 (s, 3H), 3.63 (s, 3H), 3.53 (s, 3H), 3.80–3.73 (m, 1H), 3.40 (dt, 1H, J = 4.0, J = 10.4), 2.24–2.18 (m, 1H), 2.09–1.85 (m, 1H), 1.73–1.62 (m, 1H), 1.61–1.44 (m, 2H), 1.24–1.08 (m, 2H), 0.98–0.56 (m, 3H), 0.84 (d, 3H, J = 6.6), 0.76 (d, 3H, J = 6.6), 0.70 (d, 3H, J = 6.6); ^{13}C NMR δ 194.67, 173.36, 153.45, 148.95, 148.45, 148.29, 132.85, 129.10, 125.12, 123.51, 117.26, 110.33, 109.43, 108.02, 101.45, 78.88, 69.11, 55.79, 55.55, 55.30, 55.12, 48.86, 47.43, 42.45, 39.62, 33.83, 30.93, 25.07, 22.75, 21.75, 20.72, 15.50; ^{1}H NMR δ **28**β (40%) 7.55–6.45 (m, 6H), 5.71 (d, 1H, J = 4.7), 5.44 (sbr,1H), 4.85 (d, 1H, J = 8.0), 3.91 (s, 3H), 3.89 (s, 3H), 3.82 (s, 3H), 3.66 (s, 3H), 3.40–3.15 (m, 2H), 2.24–2.18 (m, 1H), 2.09–1.85 (m, 1H), 1.73–1.62 (m, 1H), 1.61–1.49 (m, 2H), 1.24–1.08 (m, 2H), 0.98–0.56 (m, 3H), 0.82 (d, 3H, J = 6.6), 0.76 (d, 3H, J = 6.6), 0.71 (d, 3H, J = 6.6); ^{13}C NMR δ 192.98, 173.20, 154.15, 149.01, 148.63, 148.29, 131.71, 128.38, 126.00, 123.51, 118.60, 110.13, 109.61, 108.83, 100.49, 78.80, 73.51, 55.88, 55.73, 55.49, 55.36, 50.13, 47.37, 42.91, 39.55, 34.00, 31.02, 25.07, 22.65, 21.98, 20.65, 15.28; HRMS calcd 570.283, found 570.283.

(2*S*,3*S*)-2,3-Bis[(3,4-dimethoxyphenyl)hydroxymethyl]-1,4-butanediol (29). Under an N_2 atmosphere was slowly added **28** (1.0 g, 1.7 mmol) in 5 mL of THF to a stirred suspension of 270 mg (6.8 mmol, 4 equiv) of $LiAlH_4$ in 100 mL of THF. Refluxing the reaction mixture for 16 h was followed by careful addition of 5 mL of wet THF (10% H_2O) and the mixture was refluxed for 1 h. The alumina salts were continuously extracted with THF for 4 days. After drying (Na_2SO_4) and evaporation of the solvent, the *d*-menthol was removed by careful bulb-to-bulb distillation (75 °C, 0.01 mmHg) which afforded 480 mg (1.1 mmol, 67%) of the pure adduct **29** as a mixture of isomers: ^{1}H NMR (mixture of isomers) δ 7.0–6.75 (m, 6H), 4.75 (m, 1H), 4.26 (m, 1H), 3.90–3.60 (m, 8H), 3.89 (s, 6H), 3.87 (s, 6H), 3.15–3.10 (m, 2H); ^{13}C NMR δ 155.07, 152.37, 149.03, 158.91, 133.36, 132.82, 131.62, 118.10, 110.88, 110.76, 109.15, 109.06, 108.63, 87.45, 86.00, 71.60, 55.81, 55.68, 55.64; HRMS (due to H_2O elimination, MS identical to MS of eudesmin) $M^+ - H_2O$ = 404 − 18 = 386, calcd 386.173, found 386.173.

1,4-Bis(3,4-dimethoxyphenyl)tetrahydro-[1*S*-(1a,3aa,4a,6aa)]-1*H*,3*H*-furo[3,4-*c*]furan ((−)-Eudesmin, 30). To a stirred solution of **29** (200 mg, 0.47 mmol) in 40 mL of CH_2Cl_2 was added under an N_2 atmosphere at 0 °C 20 μL of BF_3·OEt_2 (48% BF_3). The clear solution became brown immediately. After stirring for 16 h at 4 °C, 30 mL of saturated $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). Subsequent washing of the organic layers with 30 mL of brine, drying (Na_2SO_4), and evaporation of the solvent was followed by chromatography (silica gel, CH_2Cl_2 followed by ether) to afford after one crystallization from MeOH pure **30** (80 mg, 44%): mp 106–108 °C; $[\alpha]^{23}_D$ −64.2 (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 6.95–6.80 (m, 6H), 4.76 (d, 2H, J = 4.2), 4.26 (dd, 2H, J = 5.8, J = 9.0), 3.90–3.87 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.15–3.05 (m, 2H); ^{13}C NMR δ 148.99, 148.26, 133.35, 118.29, 110.86, 109.04, 85.60, 71.55, 55.78, 55.76, 54.00; HRMS calcd 386.173, found 386.173.

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